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54 **Beta-lactam antibiotics.**

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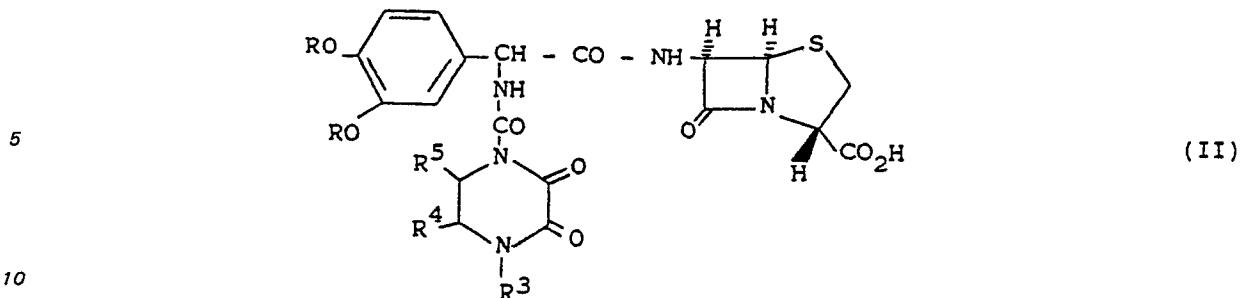
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The file contains technical information
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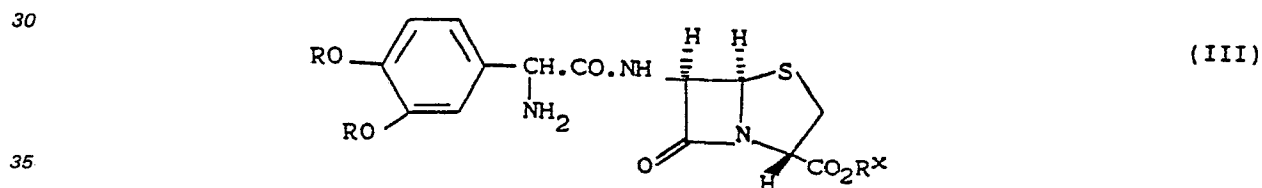
wherein R is as defined hereinbefore, R³ represents hydrogen or C₁₋₆ alkyl; R⁴ and R⁵ are the same or different and represent hydrogen, C₁₋₆ alkyl, halogen, amino, hydroxy or C₁₋₆ alkoxy.

15 Suitable C₁₋₆ alkyl groups for the groups R³, R⁴ and R⁵ include methyl, ethyl, *n*- and *iso*-propyl, *n*-, *sec*-, *iso*- and *tert*-butyl. Preferably R³ is ethyl. Preferably R⁴ and R⁵ are hydrogen.

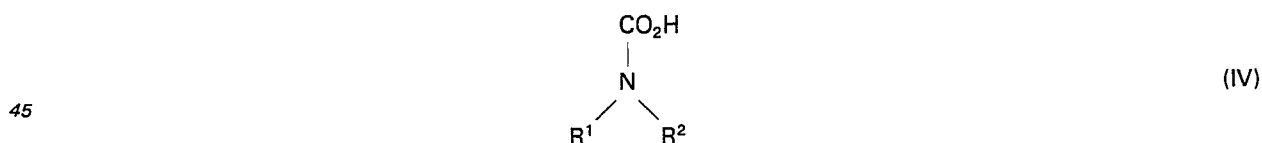
Specific compounds within this invention include the following:

- 20 6,β-[D-2-(4-ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanic acid;
- 6,β-[DL-2-(4-ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanic acid;
- 6,β-(D,L-2-[3-(3,4-diacetoxyphenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-diacetoxyphenyl)] acetamidobisnorpenicillanic acid;
- 25 6,β-(D,L-2-(3-phenylcarbonyl-3-methyl-1-ureido)-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanic acid;
- 6,β-[D-2-[3-(4-chlorophenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-dihydroxyphenyl)]-acetamidobisnorpenicillanic acid.

The compounds of formula (I) may be prepared by reacting a compound of formula (III):



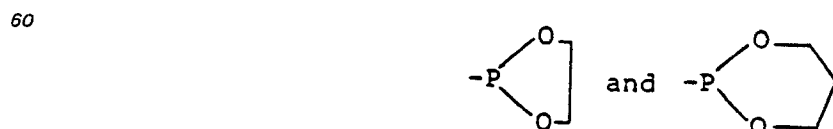
wherein R is as hereinbefore defined, the α-amino group is optionally substituted with a group which permits acylation to take place, and R^x is hydrogen or a carboxyl-blocking group, with an N-acylating derivative of an acid of formula (IV):



wherein R¹ and R² are as defined with respect to formula (I) above and any reactive groups may be protected; and thereafter, if necessary, carrying out one or more of the following steps:

- 50 i) removing any carboxyl-blocking group R^x;
- ii) removing any protecting groups on the side-chain group;
- iii) converting the product into a salt or *in vivo* hydrolysable ester thereof.

Suitable groups which permit acylation to take place and which are optionally present on the amino group of the starting material of the formula (III) include N-silyl, N-stannyl and N-phosphorus groups, for example trialkylsilyl groups such as trimethylsilyl, trialkyltin groups such as tri-*n*-butyltin, groups of formula —P.R^aR^b wherein R^a is an alkyl, haloalkyl, aryl, aralkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy or dialkylamino group, R^b is the same as R^a or is halogen or R^a and R^b together form a ring; suitable such phosphorus groups being —P(OC₂H₅)₂, —P(C₂H₅)₂, and



Suitable carboxyl-blocking derivatives for the group $-\text{CO}_2\text{R}^x$ in formula (III) include salts and ester derivatives of the carboxylic acid. The derivative is preferably one which may readily be cleaved at a later stage of the reaction. Suitable salts include metal salts, such as those with sodium, potassium and lithium, and tertiary amine salts, such as those with tri-lower-alkylamines, N-ethylpiperidine, 2,6-lutidine, pyridine, N-methylpyrrolidine, dimethylpiperazine. A preferred salt is with triethylamine.

Suitable ester-forming carboxyl-blocking groups are those which may be removed under conventional conditions. Such groups for R^x include benzyl, p-methoxybenzyl, 2,4,6-trimethylbenzyl, 3,5-di-t-butyl-4-hydroxy-benzyl, benzoylmethyl, p-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromomethyl, t-butyl, t-amyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl, tetrahydrofuran-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, p-toluenesulfonyl, methoxymethyl, a silyl, stannyl or phosphorus-containing group, such as described above, an oxime radical of formula $-\text{N}=\text{CHR}^o$ where R^o is aryl or heterocyclic, or an *in vivo* hydrolysable ester radical such as defined above.

The carboxyl group may be regenerated from any of the above esters by usual methods appropriate to the particular R^x group, for example, acid — and base — catalysed hydrolysis, or by enzymically — catalysed hydrolysis, or by hydrogenation.

A reactive N-acylating derivative of the acid (IV) is employed in the above process. The choice of reactive derivative will, of course, be influenced by the chemical nature of the substituents of the acid.

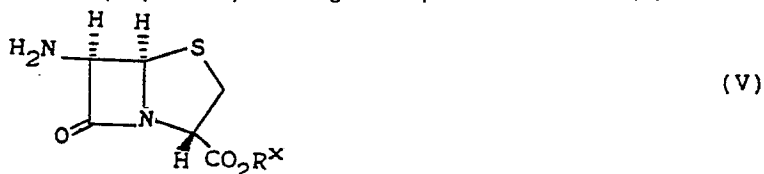
Suitable N-acylating derivatives include an acid halide, preferably the acid chloride or bromide. Acylation with an acid halide may be affected in the presence of an acid binding agent for example, tertiary amine (such as triethylamine or dimethylaniline), an inorganic base (such as calcium carbonate or sodium bicarbonate) or an oxirane, which binds hydrogen halide liberated in the acylation reaction. The oxirane is preferably a (C_{1-6}) -1,2-alkylene oxide — such as ethylene oxide or propylene oxide. The acylation reaction using an acid halide may be carried out at a temperature in the range -50°C to $+50^\circ\text{C}$, preferably -20°C to $+20^\circ\text{C}$, in aqueous or non-aqueous media such as aqueous acetone, aqueous tetrahydrofuran, ethyl acetate, dimethylacetamide, dimethylformamide, acetonitrile, dichloromethane, 1,2-dichloroethane, or mixtures thereof. Alternatively, the reaction may be carried out in an unstable emulsion of water-immiscible solvent, especially an aliphatic ester or ketone, such as methyl isobutyl ketone or butyl acetate.

Alternatively, the N-acylating derivative of the acid (IV) may be a symmetrical or mixed anhydride. Suitable mixed anhydrides are alkoxy formic anhydrides, or anhydrides with, for example, carbonic acid monoesters, trimethyl acetic acid, thioacetic acid, diphenylacetic acid, benzoic acid, phosphorus acids (such as phosphoric or phosphorous acids), sulphuric acid or aliphatic or aromatic sulphonic acids (such as p-toluenesulphonic acid). The mixed or symmetrical anhydrides may be generated using N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. When a symmetrical anhydride is employed, the reaction may be carried out in the presence of 2,4-lutidine as catalyst.

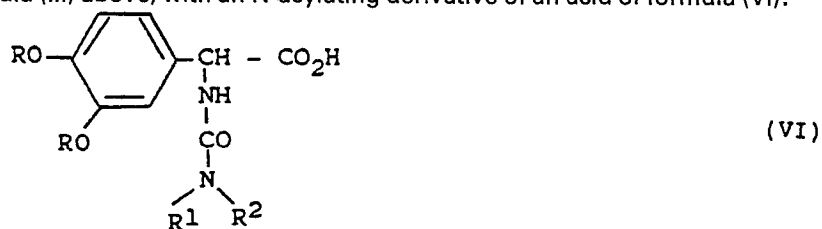
Alternative N-acylating derivatives of acid (IV) are the acid azide, or activated esters such as esters with 2-mercaptopyridine, cyanomethanol, p-nitrophenol, 2,4-dinitrophenol, thiophenol, halophenols, including pentachlorophenol, monomethoxyphenol or 8-hydroxyquinoline; or amides such as N-acylsaccharins or N-acylphthalimides; or an alkylidene iminoester prepared by reaction of the acid (IV) with an oxime.

Other reactive N-acylating derivatives of the acid (IV) include the reactive intermediate formed by reaction *in situ* with a condensing agent such as a carbodiimide, for example N,N-diethyl-, dipropyl-, or diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide or N-ethyl-N'-γ-dimethylaminopropylcarbodiimide; a suitable carbonyl compound, for example N,N'-carbonyldiimidazole or N,N'-carbonylditriazole; an isoxasolinium salt, for example N-ethyl-5-phenylisoxazolinium-2-sulphonate or N-t-butyl-5-methylisoxazolinium perchlorate; or an N-alkoxycarbonyl-2-alkoxy-1,2-dihydroquinoline, such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. Other condensing agents include Lewis acids (for example BBR_3 — C_6H_6); or a phosphoric acid condensing agent such as diethylphosphoryl-cyanide. The condensation reaction is preferably carried out in an organic reaction medium, for example methylene chloride, dimethylformamide, acetonitrile, alcohol, benzene, dioxan, or tetrahydrofuran.

The compounds of formula (I) may also be prepared by reacting a compound of formula (V):



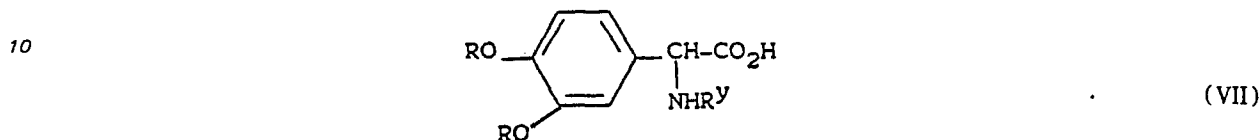
wherein the amino group is optionally substituted with a group which permits acylation to take place and R^x is as defined with respect to formula (III) above, with an N-acylating derivative of an acid of formula (VI):



wherein R, R¹ and R² are as defined with respect to formula (I) and any reactive groups therein may be protected; and thereafter, if necessary, carrying out one or more of the following steps:

- i) removing any carboxyl-blocking group R^x;
- ii) removing any protecting groups on the side-chain group;
- 5 iii) converting the product into a salt or *in vivo* hydrolysable ester thereof.

The intermediate compound of formula (III) may be prepared by reacting a compound of formula (V) as hereinbefore defined, with an N-acylating derivative of an acid of formula (VII).



15 wherein R is as defined with respect to formula (I) and any reactive groups therein may be protected and R^y is an amino-protecting group; and thereafter removing protecting group R^y.

Suitable N-acylating derivatives, carboxyl protecting groups and reaction conditions include those described hereinbefore.

20 Suitable amino-protecting groups R^y are those well-known in the art which may be removed under conventional conditions without disruption of the remainder of the molecule.

The starting material of formula (V) is disclosed in British Patent No. 1,546,622.

The antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics, and the invention therefore includes within its scope a pharmaceutical composition comprising a compound of 25 formula (I) above together with a pharmaceutical carrier or excipient.

The composition may be formulated for administration by any route, such as oral topical or parenteral. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

30 Tablets and capsules for administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine, tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The 35 tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, 40 sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

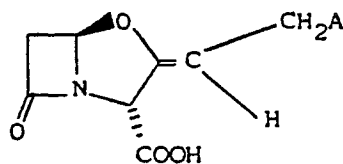
45 For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in 50 the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parental suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilized 55 by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10—60% by weight, of the active material, depending on the method of administration. Where the composition comprise dosage units, each unit will preferably contain from 50—500 mg of the active ingredient. The dosage as employed for adult 60 human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration.

The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibiotics or with a β -lactamase inhibitor may be employed.

65 Advantageously, the compositions also comprise a compound of formula (VIII) or a pharmaceutically acceptable salt or ester thereof:

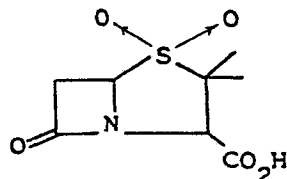
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(VIII)

wherein A is hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, mono- or di-hydrocarbyl-substituted amino, or mono- or di-acylamino.

A further advantageous composition comprises a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof together with a compound of formula (IX) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof:



(IX)

The following Examples illustrate the preparation of the compounds of this invention.

Example 1

Sodium 6,β-[D-2-(4-ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanate

a) D-2-(4-Ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-dihydroxyphenyl)acetic acid

D-3,4-Dihydroxyphenyl glycine (2.5 g, 13.7 mmol) in trimethylsilyldiethylamine (15 ml) under nitrogen was heated under reflux for 0.3 h. The solution was evaporated to dryness and the residue dissolved in dry dichloromethane (20 ml), cooled to 0°C and then treated with a solution of 4-ethyl-2,3-dioxopiperazine-1-carboxylchloride (2.7 g, 13.7 mmol) in dichloromethane (10 ml). The mixture was allowed to warm to 21°C, stirred for 1 h, poured into water (50 ml) and stirred for a further 0.2 h. The aqueous phase was basified to pH 7.5 and the organic phase then separated and discarded. Acidification of the aqueous solution to pH 1.5 with dilute hydrochloric acid followed by extraction with 10% n-butanol in ethyl acetate (3 × 50 ml), drying of the combined extracts (MgSO₄) and evaporation gave an off-white foam. This product dissolved in acetone (10 ml) was dropped into diethyl ether (100 ml) with vigorous stirring to give the title compound as a solid (1.3 g, 27%) m.p. softens above 115°C melts 140—145°C (dec), $\nu_{\max}$ (Nujol) 3300 (br), 1710, 1675, 1520 cm⁻¹ δ (d⁶-acetone) 9.8 (1H, d, *J* 7Hz, NH), 6.9 (3H, m, aryl protons), 5.4 (4H, m, reduces to 1 H, s, CHCO₂H, on the addition of D₂O, 4.2—3.3 (6H, m, CH₂—CH₂, CH₂CH₃) and 1.2 (3H, t, *J* 7Hz, CH₂CH₃) ppm.

b) D-2-(4-Ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-diacetoxyphenyl)acetic acid

D-2(4-Ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-dihydroxyphenyl) acetic acid (0.7 g, 2 mmol) in dry tetrahydrofuran (10 ml) under N₂ was cooled to 0°C when pyridine (0.48 ml, 6 mmol) and acetic anhydride (0.47 ml, 5 mmol) were added. The solution was allowed to warm to 21°C and stirred for 1.5 h. The tetrahydrofuran was then evaporated *in vacuo* and the residue partitioned between ethyl acetate and water at pH 1.5. The organic phase was separated, washed with brine, dried (MgSO₄) and evaporated to give a foam. This crude material was dissolved in dichloromethane (10 ml) and dropped into diethyl ether (100 ml) with vigorous stirring to give a solid which was filtered, washed with ether and dried (0.66 g, 77%) $\nu_{\max}$ (Nujol) 1780, 1710, 1675 cm⁻¹ δ (CD₃OD/d⁶-acetone) 10.1 (1H, d, *J* 7Hz, NH), 7.5—7.0 (3H, m, aryl protons), 5.4 (1H, d, *J* 7Hz, CH), 4.2—3.2 (6H, m, CH₂CH₂, CH₂CH₃), 2.2 (6H, s, OCOCH₃×2) and 1.1 (3H, t, *J* 7Hz, CH₂CH₃) ppm.

c) Benzyl 6β-[D,2(4-ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3-4-diacetoxyphenyl)]acetamido bisnorpenicillanate

Benzyl 6,δ-aminobisnorpenicillanate (0.28 g, 1 mmol) in dry dichloromethane (10 ml) with dicyclohexylcarbodiimide (0.21 g, 1 mmol) at 0°C was treated with D-2(4-ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-diacetoxyphenyl)acetic acid (0.43 g, 1 mmol) in dry dichloromethane (10 ml). The mixture was allowed to warm to 21°C and stirred for 2.5 h when precipitated urea was removed by filtration. The filtrate was washed with dilute hydrochloric acid, dilute sodium bicarbonate, brine then dried (MgSO₄) and evaporated to give a yellow foam. This crude material was columned on silica eluting with ethyl acetate to give the product as a foam (0.32 g, 46%) $\nu_{\max}$ (DCM) 1790, 1775, 1740, 1720, 1690, 1500, 1215 and 1190 cm⁻¹; δ (CDCl₃/d₆ acetone) 10.0 (1H, d, *J* 7Hz, NH), 8.1 (1H, d, *J* 8Hz, NH), 7.4—7.0 (8H, aryl protons), 5.7—4.9 (6H, H—6, H—5, H—3, C—H, CH₂), 4.2—3.3 (8H, m, CH₂—CH₂, CH—CH₃, H—2×2), 2.2 (6H, s, OCOCH₃×2) and 1.2 (3H, t, *J* 7Hz, CH₂CH₃) ppm.

d) Sodium 6,β-[D-2(4-ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-diacetoxyphenyl)]acetamidobisnorpenicillanate

Benzyl 6,δ-[D-2(4-ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-diacetoxyphenyl)]acetamidobisnorpenicillanate (0.18 g, 0.26 mmol) in tetrahydrofuran (10 ml) and water (4 ml) was hydrogenated for one hour in the presence of 10% palladium on charcoal (0.2 g). The mixture was filtered through celite (registered trade mark) and the filtrate evaporated to near dryness. The residue was partitioned between ethyl acetate and water at pH 6.5, the aqueous phase separated and freeze-dried to give the product as a white powder (0.1 g, 62%), $v_{\max}$ (Nujol) 1770, 1720, 1680 and 1610 cm^{-1} ; $\delta(\text{D}_2\text{O})$ 7.49 (1H, dd, J 7 Hz and 1.5 Hz, H—5'), 7.42 (1H, d, J 1.5 Hz, H—2'), 7.33 (1H, d, J 7 Hz, H—6'), 5.56 (1H, s, CH), 5.42 (1H, d, J 4 Hz, H—6), 5.27 (1H, d, J 4 Hz, H—5), 4.88 (H—3 masked by solvent), 4.00 (2H, m, N—CH₂CH₂), 3.75—3.26 (6H, m, N—CH₂, CH₂CH₃, H—2x2), 2.33 (6H, s, OCOCH₃x2) and 1.19 (3H, t, J 7 Hz, CH₂CH₃) ppm.

e) Sodium 6,β-[D-2(4-ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanate

Sodium 6,β-[D-2(4-ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-diacetoxyphenyl)]acetamidobisnorpenicillanate (20 mg, 0.032 mmol) in water (10 ml) was treated with dilute sodium bicarbonate solution until the pH had risen to 7.5. The enzyme subtilisin A on a polymer support (200 mg) was added and the mixture stirred at 21°C for 2.5 h when the mixture was filtered, the filtrate acidified to pH 1.5 and extracted with ethyl acetate (4 × 20 ml). The combined extracts were washed (brine), dried (MgSO₄) and evaporated to give the product as a colourless solid which was dissolved in water at pH 6.5 and freeze-dried to give the title compound as a white powder (8 mg, 46%) $v_{\max}$ (Nujol) 1770, 1720, 1685 and 1615 cm^{-1} ; $\delta(\text{D}_2\text{O})$ 7.15—6.92 (3H, m, aryl protons;), 5.49 (1H, s, CH), 5.35—5.28 (2H, m, H—6, H—5), 4.90 (1H, m, H—3), 4.02 (2H, m, CH₂CH₂), 3.71 (2H, m, CH₂CH₂), 3.50 (2H, q, J 7 Hz, CH₂CH₃), 3.38 (2H, m, H—2x2) and 1.19 (3H, t, J 7.5 Hz, CH₂CH₃) ppm.

Example 2

Sodium 6,β[D,L-2(4-ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanate

The title compound was prepared employing an analogous sequence of reactions as described in Example 1 starting from DL—3,4-dihydroxyphenylglycine.

Example 3

Sodium 6,β[D-2-(4-ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanate

a) D-2-(4-Ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-dihydroxyphenyl) acetic acid

D-3,4-Dihydroxyphenyl glycine (0.92 g, 5 mmol) in 1,1,1,3,3,3-hexamethyl-disilazane (8 ml) and trimethylsilyl chloride (2 ml) was heated, in an inert atmosphere, under reflux for 2 hours. Excess silylating agents and by products were removed by evaporation *in vacuo* and the residue was dissolved in dry dichloromethane (10 ml). The solution was cooled to 0°C when 4-ethyl-2,3-dioxopiperazine-1-carboxyl chloride (1.02 g, 5 mmol) in dry dichloromethane (5 ml) was added. The mixture was stirred for 1.5 hours at 21°C, evaporated to low bulk and the residue dissolved in 2:1 acetone/water (30 ml) at pH 1.5 with vigorous stirring. After 0.3 hours the acetone was evaporated, the residue basified to pH 7.5 with dilute sodium bicarbonate and washed with ethyl acetate. The aqueous phase was saturated with sodium chloride, layered with ethyl acetate and acidified to pH 2 with dilute hydrochloric acid. The aqueous phase was separated, extracted several times with ethyl acetate and the combined organic phases, washed with brine dried (MgSO₄) and evaporated to give a white solid (0.7 g, 40%). IR $v_{\max}$ (Nujol) 3300 (br), 2950 (br), 1720, 1690 cm^{-1} Pmr $\delta(\text{d}^6\text{acetone}/\text{D}_2\text{O})$ 6.9 (3H, m, aryl protons), 5.4 (1H, s, CH), 4.3—3.4 (6H, m, CH₂CH₂, CH₂CH₃) and 1.3 (3H, t, CH₂CH₃) ppm.

(b) Sodium D-2-(4-ethyl-2,3-dioxopiperazin-1-carboxylamino)-2-(3,4-dihydroxyphenyl)acetate

The acid (0.5 g, 1.4 mmol) from example 3(a) was partitioned between ethyl acetate and water at pH 6.5. The aqueous phase was separated and freeze-dried to give the sodium salt as a white amorphous solid which was dried over phosphorous pentoxide *in vacuo* (0.45 g, 85%).

IR $v_{\max}$ (Nujol) 3300 (br) 1715, 1695 and 1600 cm^{-1}

(c) Benzyl 6,β-[D-2-(4-ethyl-2,3-dioxopiperazine-1-carboxylamino)-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanate

The sodium salt (0.22 g, 0.6 mmol) from example 3(b) in dry tetrahydrofuran (10 ml) was cooled to -10°C when N-methylmorpholine (2 drops) and then methyl chloroformate (0.045 ml, 0.6 mmol) were added. The mixture was stirred for 0.75 hours, evaporated to low bulk, diluted with dry dichloromethane (5 ml) and added to a stirred solution of benzyl 6β-aminobisnorpenicillanate (0.16 g, 0.6 mmol) in dry dichloromethane (5 ml). After 2 hours the solution was washed with dilute hydrochloric acid, dilute sodium bicarbonate solution, brine, then dried (MgSO₄) and evaporated to give a foam (0.23 g).

This crude material was columned rapidly on silica gel eluting with 10% methanol, in ethyl acetate to give the product as a white foam (0.11 g, 31%).

Ir $\nu_{\max}$ (DCM) 330(b) 1795, 1745, 1715, 1690 1185^{-1} Pmr δ (CDCl₃) 7.35 (5H, m, aryl protons), 6.82 (3H, m, 3,4-dihydroxyphenyl protons), 5.60 (1H, d, H—6), 5.29 (1H, s, CH), 5.27 (1H, d, H—5), 5.19 (2H, s, CH₂), 4.95 (1H, t, H—3), 4.00 (2H, m, CON—CH₂), 3.55 (4H, m, CH₂CH₃ CH₂CH₂), 3.35 (2H, d, H—2x2) and 1.22 (3H, t, CH₂CH₃) ppm.

(d) Sodium 6,β-[D-2-(4-ethyl-2,3-dioxopiperazine-1-carbonylamino)-2-(3,4-dihydroxyphenyl)]acetamido bisnorpenicillanate

The ester (0.1 g, 0.16 mmol) from example 3(c) in tetrahydrofuran (5 ml) with 10% palladium on charcoal (0.1 g) was hydrogenated for 0.75 h. More catalyst (0.1 g) was added and hydrogenolysis continued for a further 0.75 h. The mixture was filtered through 'Celite' (registered trade mark), evaporated and the residue partitioned between ethyl acetate and water at pH 6.5. The aqueous phase was separated and freeze-dried to give an amorphous white solid (0.05 g, 56%).

Ir $\nu_{\max}$ (Nujol) 3340 (br) 1775, 1720, 1680 cm^{-1} Pmr δ (D₂O) 7.00—6.86 (3H, m, aryl protons), 5.48 (1H, d, H—6), 5.34 (1H, s, CH), 5.28 (1H, d, H—5), 4.82 (1H, masked by solvent, H—3), 4.05—3.95 (2H, m, CONCH₂), 3.75—3.62 (2H, m, CH₂CH₃, CH₂—CH₂), 3.54—3.45 (2H, m, CH₂CH₂), 3.39—3.25 (2H, ddd, H—2x2) and 1.18 (3H, t, CH₂CH₃) ppm.

Example 4

Sodium 6,β-[D,L-2-[3-(3,4-diacetoxyphenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-diacetoxyphenyl)]acetamidobisnorpenicillanate

(a) D,L-2-[3-(3,4-diacetoxyphenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-diacetoxyphenyl)acetic acid

D,L-Dihydroxyphenylglycine (0.37 g, 2 mmol) was heated under reflux in trimethylsilyldiethylamine (5 ml) for 0.25 hours to give a clear solution. Excess silylating agent and by-products were removed by evaporation *in vacuo* and the residue dissolved in dry dichloromethane (5 ml). This solution was cooled to 0°C, treated with triethylamine (0.25 ml, 2 mmol) and then with a solution of N-methyl-3,4-diacetoxybenzamide-N-carbonyl chloride (0.62 g, 2 mmol) in dry dichloromethane (10 ml). The mixture was allowed to warm to 21°C, stirred for 2 hours and then evaporated to low bulk. The residue was dissolved in methanol (10 ml) and acidified to pH 1.5 with dilute hydrochloric acid and stirred for 0.5 hours. The solution was evaporated, the residue partitioned between ethyl acetate and water and the organic phase separated, washed with brine, dried (MgSO₄) and evaporated to give a foam (0.83 g, 88%).

This material, D,L-2-[3-(3,4-diacetoxyphenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-dihydroxyphenyl)acetic acid, (0.83 g, 1.8 mmol) in dry tetrahydrofuran (10 ml) at 0°C was treated with pyridine (0.51 ml, 6.3 mmol) and acetic anhydride (0.51 ml, 5.4 mmol). The solution was allowed to warm to 21°C and was stirred for 1.5 hours. The residue obtained after evaporation was partitioned between ethyl acetate and water at pH 1.5, the organic phase being separated, washed with brine, dried (MgSO₄) and evaporated to give a foam. This material was stirred vigorously in water as the pH was adjusted to 7.2 with sodium bicarbonate solution the aqueous phase was washed with ethyl acetate then acidified to pH 2 with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was separated, washed with brine, dried (MgSO₄) and evaporated to give a white foam (0.46 g, 47%) Ir $\nu_{\max}$ (DCM) 1775, 1705, 1680—1660 (b), 1205 cm^{-1} .

Pmr δ (d⁶-acetone) 10.0 (1H, d, NH), 9.5 (1H, s, CO₂H), 7.6—7.1 (6H, complex, aryl protons), 5.6 (1H, d, CH), 3.1 (3H, s, NCH₃) and 2.3 (12H, s, OCOCH₃ × 4) ppm.

(b) Benzyl 6,β-[D,L-2-[3-(3,4-diacetoxyphenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-diacetoxyphenyl)]acetamidobisnorpenicillanate

The above acid (0.28 g, 0.5 mmol) from Example 4(a) in dichloromethane (5 ml) was added, at 0°C, to a stirred solution of benzyl 6β-aminobisnorpenicillanate (0.14 g, 0.5 mmol) and dicyclohexylcarbodiimide (0.11 g, 0.5 mmol), in dry dichloromethane (7 ml). The mixture was allowed to warm to 21° and was stirred for 2 hours. Solid material was filtered off and the filtrate washed with dilute hydrochloric acid, dilute sodium bicarbonate solution, brine, then dried (MgSO₄) and evaporated to give a semi-solid material (0.4 g) which was columned on silica eluting with 1:1 *n*-hexane/ethyl acetate to give the product as a colourless glass (0.2 g, 49%).

Ir $\nu_{\max}$ (DCM) 1790 (sh) 1780, 1710—1690 (br) 1200 cm^{-1} . Pmr δ (CDCl₃) 10.00 (1H, d, NH), 7.45—7.20 (11H, complex, aryl protons), 6.75 (1H, d, NH), 5.58 (2H, m, H—6, CH), 5.34 (1H, d, H—5), 5.19 (2H, ABq, CH₂), 4.98 (1H, m, H—3), 3.41—3.26 (2H, m, H—2, × 2), 3.22 (3H, s, NCH₃) and 2.30 (12H, s, OCOCH₃ × 4) ppm.

(c) Sodium 6,β-[DL-2-[3-(3,4-diacetoxyphenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-diacetoxyphenyl)]acetamido bisnorpenicillanate

The above ester (0.17, 0.21 mmol) from Example 4(b) dissolved in tetrahydrofuran (5 ml) with 10% palladium on charcoal (0.17 g) was shaken under an atmosphere of hydrogen for 1 hour. The mixture was filtered through 'Celite' (registered trade mark), evaporated and the residue partitioned between water at pH 6.5 and ethyl acetate. The aqueous phase was separated and freeze-dried to give the title compound as a white solid (0.098 g, 73%).

Ir $\nu_{\max}$ (Nujol) 3300, 1775, 1700, 1660, 1600 cm^{-1} . Pmr δ (d^6 acetone/ CD_3OD) 7.5—7.1 (6H, m, aryl protons), 5.7—5.1 (4H, m, H—6, H—3, CH), 3.6—3.3 (2H, m, H—2 $\times$ 2), 3.2 (3H, s, NCH_3), and 2.3 (12H, s, $\text{OCOCH}_3 \times 4$) ppm.

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Example 5

Sodium 6, β -[D,L-2-(3-phenylcarbonyl-3-methyl-1-ureido)-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanate

(a) D,L-2-(3-Phenylcarbonyl-3-methyl-1-ureido)-2-(3,4-dihydroxyphenyl) acetic acid

N-Methylbenzamide (0.41 g, 3 mmol) with 4-N,N-dimethylaminopyridine (0.1 g, 0.8 mmol) in dry dichloromethane (4 ml) was treated with triethylamine (0.42 ml, 3 mmol) and then trimethylsilyl chloride (0.38 ml, 3 mmol) for 0.5 hours at 21°. The solution was then heated under reflux for 0.5 hours, cooled, evaporated to ca 1 ml and diluted with dry dichloromethane (5 ml). The solution was cooled to 0°, treated with triethylamine (0.42 ml, 3 mmol) and then phosgene (3 ml of 12.5% solution in toluene) and stirred for 0.45 hours at 0—10°. The mixture was then evaporated to ca 2 ml and diluted with dichloromethane (5 ml).

DL,3,4-Dihydroxyphenylglycine (0.55 g, 3 mmol) was heated under reflux in trimethylsilyldiethylamine (8 ml) for 0.25 hours. Excess silylating agent and by products were removed by evaporation *in vacuo* and the persilylated residue dissolved in dry dichloromethane (5 ml). This solution was cooled to 0° and treated with the above N-carbonyl chloride preparation. The mixture was allowed to warm to 21° and was stirred for 2 hours when water (15 ml) and acetone (30 ml) were added. The solution was adjusted to pH 1.5 with 5N hydrochloric acid and stirred vigorously for 0.5 hours when the organic solvents were evaporated *in vacuo*. The residue was basified to pH 8 with dilute sodium bicarbonate solution and washed with ethyl acetate. The separated aqueous phase was layered with ethyl acetate and acidified to pH 1.5 with dilute hydrochloric acid. The organic layer was separated, washed with brine, dried (MgSO_4) and evaporated to give a yellow foam (0.7 g, 68%).

Ir $\nu_{\max}$ (Nujol) 3700—2500 (br), 1740 (sh) 1690 cm^{-1} . Pmr δ (CDCl_3/d^6 acetone) 10.0 (1H, d, NH), 8.5 (3H, br s, $\text{OH} \times 2$, CO_2H), 7.4 (5H, s, aryl protons), 6.9 (3H, m, 3,4-dihydroxyphenyl protons), 5.5 (1H, d, CH) and 3.2 (3H, s, N—CH_3).

(b) Benzyl 6, β -[D,L-2-(3-phenylcarbonyl-3-methyl-1-ureido)-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanate

The above acid (0.2 g, 0.58 mmol) from Example 5(a) in dry tetrahydrofuran (5 ml) was cooled to -15° when N-methylmorpholine (0.064 ml, 0.58 mmol) and methylchloroformate (0.045 ml, 0.08 mmol) was added. The mixture was stirred for 0.75 hours at 0°, concentrated to ca 2 ml and diluted with dry dichloromethane (4 ml). This solution was added, at 0° to a stirred solution of benzyl 6 β -aminobisnorpenicillanate (0.16 g, 0.58 mmol) in dry dichloromethane (5 ml). Stirring was continued for 1.75 hours during which time the temperature was allowed to rise to ambient. The solution was washed with dilute hydrochloric acid, dilute sodium bicarbonate solution, brine and was then dried (MgSO_4) and evaporated to give a foam (0.28 g). This crude product was columned on silica gel eluting with 1:2 *n*-hexane/ethyl acetate to give the desired ester as a colourless gum (0.12 g, 37%).

Ir $\nu_{\max}$ (DCM) 1795, 1750, 1715 (sh) 1695 cm^{-1} . Pmr δ ($\text{CDCl}_3/\text{CD}_3\text{OD}$) 7.4 (5H, s, aryl protons), 7.3 (5H, s, aryl protons), 6.8 (3H, m, 3,4-dihydroxyphenyl), 5.6 (1H, d, H—6), 5.4 (1H, s, CH), 5.25 (1H, d, H—5), 5.2 (2H, s, CH_2), 5.0 (1H, m, H—3), 3.4 (2H, m, H—2 $\times$ 2) and 3.1 (3H, s, NCH_3) ppm.

(c) Sodium 6, β -[D,L-2-(3-phenylcarbonyl-3-methyl-1-ureido)-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanate

The above ester (0.1 g, 0.16 mmol) from Example 5(b) in tetrahydrofuran (5 ml) with 10% palladium on charcoal (0.1 g) was shaken under an atmosphere of hydrogen for 0.5 hours. More catalyst (0.1 g) was added and hydrogenolysis continued for a further 0.75 hours. The mixture was filtered through 'Celite' (registered trade mark) evaporated and the residue partitioned between ethyl acetate and water at pH 6.7. The aqueous phase was separated and freeze-dried to give the title compound as a white solid (0.06 g, 70%).

Ir $\nu_{\max}$ (Nujol) 3600—3100 (br), 1780, 1710 (sh) 1690, 1600 cm^{-1} , Pmr δ ($\text{CD}_3\text{OD}/\text{D}_2\text{O}$) 7.5 (5H, s, aryl protons), 6.8 (3H, m, 3,4-dihydroxyphenyl protons), 5.5 (1H, d, H—6), 5.25 (2H, m, H—5, CH), 4.7 (H—3 masked by solvent), 3.3 solid (H—2 $\times$ 2, masked by solvent) and 3.1 (3H, s, NCH_3) ppm.

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Example 6

Sodium 6, β -[D-2-[3-(4-chlorophenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanate

(a) D-2-[3-(4-chlorophenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-dihydroxyphenyl)acetic acid

This acid was prepared using a procedure analogous to that described in example 5(a). Thus 4-chloro-N-methylbenzamide (0.51 g, 3 mmol) gave the title acid as a foam (1.1 g, 96%).

Ir $\nu_{\max}$ (Nujol) 3600—3200 (br), 1720 (sh), 1690, 1510, 1100, 1045, 1020 cm^{-1} , Pmr δ ($\text{CDCl}_3/\text{CD}_3\text{OD}$) 9.9 (1H, d, NH), 7.4 (4H, s, *p*-chlorophenyl protons), 6.9 (3H, m, 3,4-dihydroxyphenyl protons), 5.4 (1H, d, CH) and 3.2 (3H, s, NCH_3) ppm.

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(b) Benzyl 6,β-[D,2-[3-(4-chlorophenylcarbonyl)-3-methyl-(1-ureido)-2-(3,4-dihydroxyphenyl)]acetamidobis-norpenicillanate.

This ester was prepared from the reaction of D,2-[3-(4-chlorophenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-dihydroxyphenyl)acetic acid (0.38 g, 1 mmol) and benzyl 6 β -aminobisnorpenicillanate (0.28 g, 1 mmol) using a method analogous to that described in example 5(b). The yield was 0.3 g, 47%.

Ir ν_{max} (DCM) 3300 (br), 1790, 1750, 1690, 1510, 1340, 1095, 1045, 1020 cm^{-1} , Pmr δ ($\text{CDCl}_3/\text{CD}_3\text{OD}$) 7.4 (4H, s, p-chlorophenyl protons), 7.2 (5H, s, benzyl protons), 6.9 (3H, m, 3,4-dihydroxyphenyl protons), 5.5 (2H, m, H—6, CH), 5.2 (1H, d, H—5 superimposed upon 2H, s, CH_2), 4.8 (1H, m, H—3), 3.3 (2H, m, H—2x2) and 3.1 (3H, s, NCH_3) ppm.

(c) Sodium 6,β-[D,2-[3-(4-chlorophenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanate.

The ester (0.1 g, 0.16 mmol) from example 6(b) was deprotected using an analogous procedure to that described in example 5(c) to give the title compound as a white solid (0.03 g, 32%).

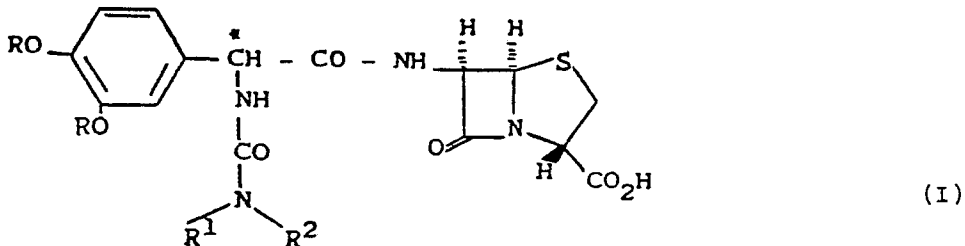
Ir ν_{max} (Nujol) 3600—3200 (br), 1780, 1720 (sh), 1700, 1610, 1100, 1060, 1030 cm^{-1} $\delta(\text{CD}_3\text{OD})$ 7.53, 7.45 (4H, ABq, p-chlorophenyl protons), 6.89—6.70 (3H, m, 3,4-dihydroxyphenyl protons), 5.51 (1H, d, H—6), 5.35 (1H, s, CH), 5.23 (1H, d, H—5), 4.72 (1H, dd, H—3), 3.40—3.30 (2H, m, H—2x2) and 3.18 (3H, s, NCH_3) ppm.

Biological Data — Antibacterial In Vitro Activity

Compound of Example 3	(MIC mg/ml)
E.coli ESS	0.02
E.coli JT4	1.0
E.coli JT425	0.05
E.coli NCTC 10418	0.02
Ps. aeruginosa NCTC 10662	1.0
Ps. aeruginosa NCTC 10662 10^{-2}	0.1
Ps. aeruginosa Dalglish 10^{-2}	2.5
S. marcesens US32	0.2
K. aerogenes A	0.05
E. cloacae NI	0.5
P. mirabilis C977	0.1
P. mirabilis 899	100
P. rettgeri	0.2
S. aureus Oxford	5.0
S. aureus Russell	50
N. catarrhalis 1502	0.02
S. faecalis I	50
S. pyogenes CN10	0.5

Claims

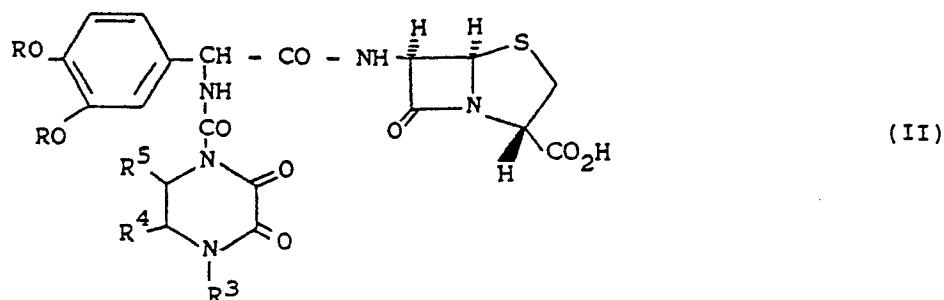
1. A compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof:



wherein R is hydrogen, C₁₋₆ alkylcarbonyl; R¹ is hydrogen or a C₁₋₆ alkyl; R² is hydrogen, a C₁₋₆ alkyl optionally substituted by heterocyclyl, a heterocyclic group, or CXR^d where X is O or S and R^d is hydrogen, C₁₋₆ alkyl optionally substituted by heterocyclyl, or a heterocyclyl group; or R¹ and R² together with the nitrogen to which they are attached form a heterocyclyl group; the aforementioned heterocyclyl groups comprising single or fused rings having up to four hetero atoms in the ring selected from oxygen, nitrogen and sulphur and optionally substituted with up to three halogen, C₁₋₆alkyl, C₁₋₆ alkoxy, halo-(C₁₋₆)-alkyl, hydroxy, amino, carboxy, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkoxycarbonyl(C₁₋₆)alkyl, oxo, phenyl optionally substituted with up to three groups selected from halogen, C₁₋₆ alkyl, phenyl, C₁₋₆ alkoxy, halo(C₁₋₆)alkyl, hydroxy, amino, nitro, carboxy, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkoxycarbonyl (C₁₋₆)alkyl, C₁₋₆ alkoxycarbonyloxy, or C₁₋₆ alkylcarbonyl, or naphthyl, optionally substituted as for phenyl, groups.

2. A compound as claimed in claim 1 wherein R is hydrogen or acetyl.

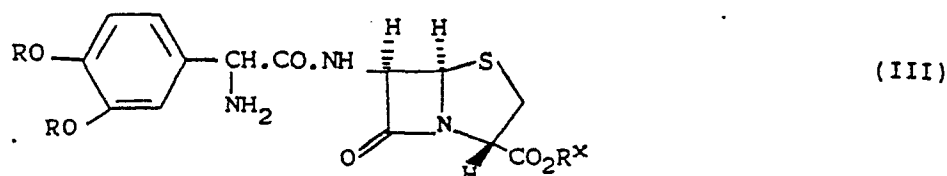
3. A compound as claimed in either of claims 1 or 2 wherein R¹ is hydrogen or C₁₋₆ alkyl.
 4. A compound as claimed in claim 3 wherein R² is a group COR^d wherein R^d is as defined in claim 1.
 5. A compound of formula (II) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof:



wherein R is as defined in claim 1, R³ represents hydrogen or C₁₋₆ alkyl; R⁴ and R⁵ are the same or different and represent hydrogen, C₁₋₆ alkyl, halogen, amino, hydroxy or C₁₋₆ alkoxy.

6. 6β-[D-2-(4-Ethyl-2,3-dioxopiperazine-1-carbonylamino)-2-(3,4-dihydroxyphenyl)]acetamidobis-norpenicillanic acid;
 6β-[D,L-2-(4-ethyl-2,3-dioxopiperazine-1-carbonylamino)-2-(3,4-dihydroxyphenyl)]acetamidobis-norpenicillanic acid;
 6,β-[D,L-2-[3-(3,4-diacetoxyphenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-diacetoxyphenyl)]acetamidobisnorpenicillanic acid;
 6,β-[D,L-2-(3-phenylcarbonyl-3-methyl-1-ureido)-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanic acid;
 6,β-[D-2-[3-(4-chlorophenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillanic acid or pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof.

7. A process for the preparation of a compound as claimed in claim 1, which process comprises:
 A) reacting a compound of formula (III):



wherein R is as defined in claim 1, the α-amino group is optionally substituted with a group which permits acylation to take place, and R^x is hydrogen or a carboxyl-blocking group, with an N-acylating derivative of an acid of formula (IV):

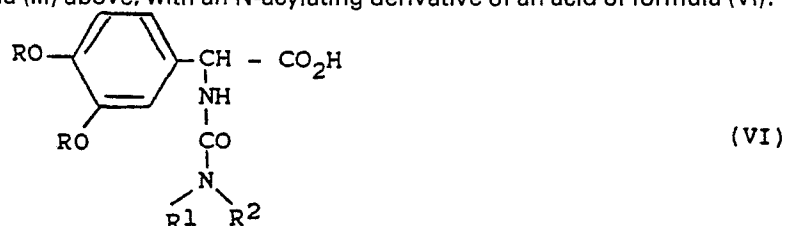


wherein R¹ and R² are as defined in claim 1 any reactive groups may be protected;

- B) reacting a compound of formula (V):



wherein the amino group is optionally substituted with a group which permits acylation to take place and R^x is as defined with respect to formula (III) above, with an N-acylating derivative of an acid of formula (VI):

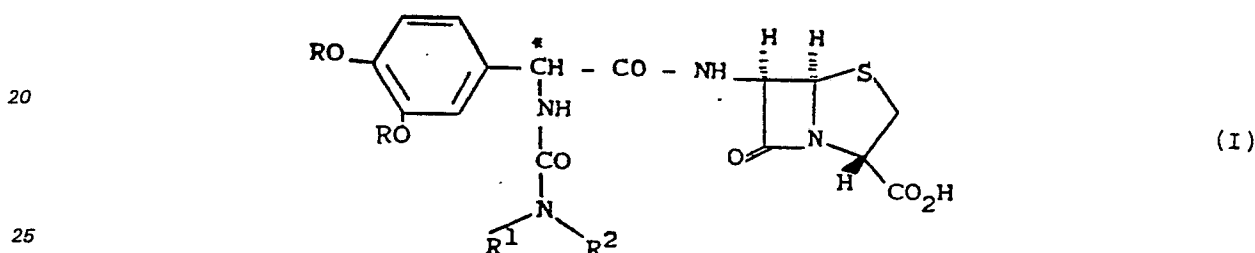


wherein R, R¹ and R² are as defined with respect to formula (I) and any reactive groups therein may be protected; and after steps A or B, if necessary, carrying out one or more of the following steps:

- i) removing any carboxyl-blocking group R^{*};
 - ii) removing any protecting groups on the side-chain group;
 - iii) converting the product into a salt or in vivo hydrolysable ester thereof.
8. A composition which comprises a compound as claimed in any of claims 1 to 6 together with a pharmaceutically acceptable carrier or excipient.
9. A composition as claimed in claim 8 which also comprises a β -lactamase inhibitor.
10. A compound as claimed in any one of claims 1 to 6 for use in the treatment of antibacterial infections in the human or animal body.

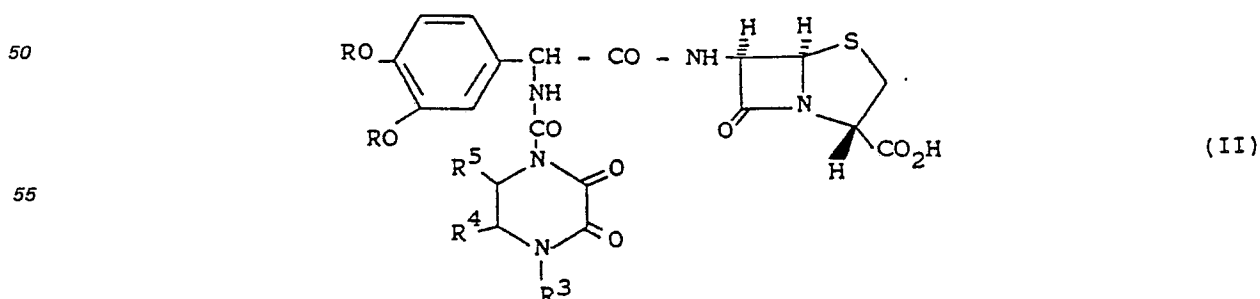
Patentansprüche

1. Eine Verbindung der Formel (I) oder ein pharmazeutisch verträgliches Salz oder ein in-vivo hydrolysierbarer Ester davon:



in welcher R Wasserstoff oder C₁₋₆-Alkylcarbonyl, ist; R¹ Wasserstoff oder ein C₁₋₆-Alkyl ist; R² Wasserstoff, ein C₁₋₆-Alkyl, gegebenenfalls substituiert durch Heterocyclyl, eine heterocyclische Gruppe oder eine Gruppe CXR^d, in welcher X Sauerstoff oder Schwefel bedeutet und R^d Wasserstoff, C₁₋₆-Alkyl, gegebenenfalls substituiert durch Heterocyclyl, oder eine heterocyclische Gruppe bedeutet; oder R¹ und R² zusammen mit dem Stickstoffatom, an das sie gebunden sind, eine heterocyclische Gruppe bilden, wobei die vorstehend genannten heterocyclischen Gruppen einzelne oder miteinander kondensierte Ringe mit bis zu 4 Heteroatomen in der Ringstruktur enthalten, ausgewählt aus Sauerstoff, Stickstoff und Schwefel und welche gegebenenfalls substituiert sind, mit bis zu drei Gruppen ausgewählt aus Halogen, C₁₋₆-Alkyl, C₁₋₆-Alkoxy, Halo-(C₁₋₆)-alkyl, Hydroxy, Amino, Carboxy, C₁₋₆-Alkoxy-carbonyl, C₁₋₆-Alkoxy-carbonyl (C₁₋₆)-alkyl, Oxo oder Phenyl, letzteres gegebenenfalls substituiert mit bis zu drei Gruppen ausgewählt aus Halogen, C₁₋₆-Alkyl, Phenyl, C₁₋₆-Alkoxy, Halo(C₁₋₆)-alkyl, Hydroxy, Amino, Nitro, Carboxy, C₁₋₆-Alkoxy-carbonyl, C₁₋₆-Alkoxy-carbonyl(C₁₋₆)-alkyl, C₁₋₆-Alkoxy-carbonyloxy, oder C₁₋₆-Alkylcarbonyl, oder Naphthyl, gegebenenfalls substituiert durch die für Phenyl aufgeführten Substituenten.

2. Eine Verbindung wie in Anspruch 1 beansprucht, in welcher R Wasserstoff oder Acetyl ist.
3. Eine Verbindung wie in einem der beiden Ansprüche 1 oder 2 beansprucht, in welcher R¹ Wasserstoff oder C₁₋₆-Alkyl ist.
4. Eine Verbindung wie in Anspruch 3 beansprucht, in welcher R² eine Gruppe COR^d ist, wobei R^d wie in Anspruch 1 definiert ist.
5. Eine Verbindung der Formel (II) oder ein pharmazeutisch verträgliches Salz oder ein in-vivo hydrolysierbarer Ester derselben:



in welcher R wie in Anspruch 1 definiert ist, R³ Wasserstoff oder C₁₋₆-Alkyl bedeutet; R⁴ und R⁵ gleich oder verschieden sind und Wasserstoff, C₁₋₆-Alkyl, Halogen, Amino, Hydroxy, Hydroxy oder C₁₋₆-Alkoxy bedeuten.

6. 6 β -[D-2-(4-Äthyl-2,3-dioxopiperazin-1-carbonylamino)-2-(3,4-dihydroxyphenyl)]acetamidobisnor-penicillansäure;

6 β -[D,L-2-(4-Äthyl-2,3-dioxopiperazin-1-carbonylamino)-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillansäure;

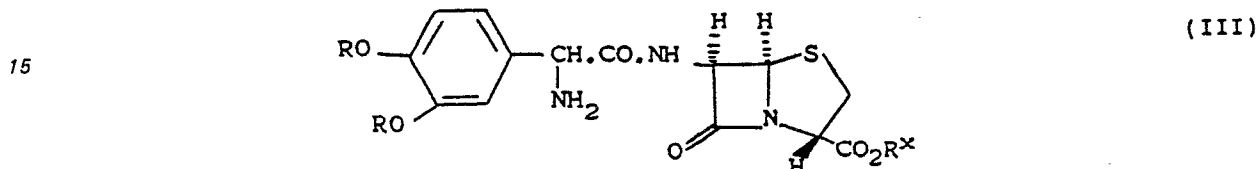
6, β -[D,L-2-[3-(3,4-Diacetoxyphenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-diacetoxyphenyl)]acetamidobisnorpenicillan-säure;

5 6, β -[D,L-2-(3-Phenylcarbonyl-3-methyl-1-ureido)-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillansäure;

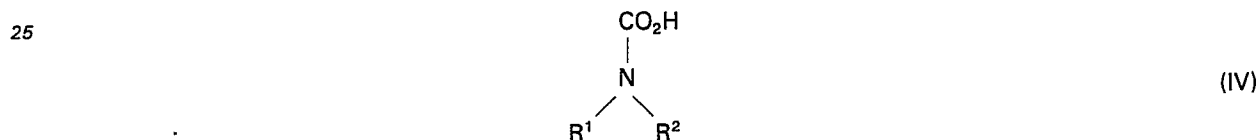
6, β -[D-2-[3-(4-Chlorophenylcarbonyl)-3-methyl-1-ureido]-2-(3,4-dihydroxyphenyl)]acetamidobisnorpenicillansäure oder pharmazeutisch verträgliche Salze oder in vivo hydrolysierbare Ester davon.

7. Ein Verfahren zur Herstellung einer Verbindung wie in Anspruch 1 beansprucht, welches Verfahren
10 umfaßt:

A) die Umsetzung einer Verbindung der Formel (III):

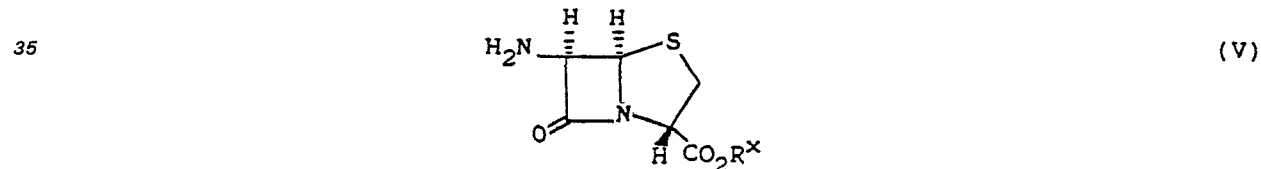


20 in welcher R wie in Anspruch 1 definiert ist, die α -Aminogruppe gegebenenfalls durch eine Gruppe substituiert ist, welche eine Acylierungsreaktion zuläßt, und R^x Wasserstoff oder eine Carboxyl-Hemmgruppe bedeutet, mit einem N-acylierenden Derivat einer Säure der Formel (IV):

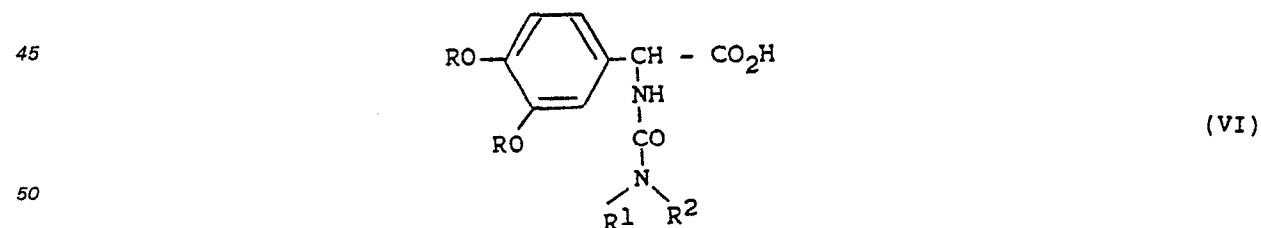


30 in welcher R¹ und R² wie in Anspruch 1 definiert sind und jede reaktive Gruppe geschützt sein kann;

B) die Umsetzung einer Verbindung der Formel (V):



40 in welcher die Aminogruppe gegebenenfalls substituiert ist durch eine Gruppe, welche eine Acylierung zuläßt, und R^x wie in bezug auf Formel (III) definiert ist, mit einem N-acylierenden Derivat einer Säure der Formel (VI):



50 in welcher R, R¹ und R² wie in bezug auf Formel (I) definiert sind und alle enthaltenen reaktiven Gruppen geschützt sein können; und anschließend nach den Stufen A) und B), falls notwendig, die Durchführung einer oder mehrerer der folgenden Schritte:

- i) Entfernen jeglicher Carboxyl-Hemmgruppen R^x;
- ii) Entfernen jeglicher Schutzgruppen an den Seitenkettengruppen;
- iii) Umwandlung des Produkts in ein Salz oder einen in vivo hydrolysierbaren Ester desselben.

8. Eine Zusammensetzung welche eine Verbindung wie in Aneinem der Ansprüche 1 bis 6 beansprucht
60 zusammen mit einem pharmazeutisch verträglichen Träger oder Arzneimittelträger enthält.

9. Eine Zusammensetzung wie in Anspruch 8 beansprucht, welche zusätzlich eine β -Lactamase-Hemmsubstanz enthält.

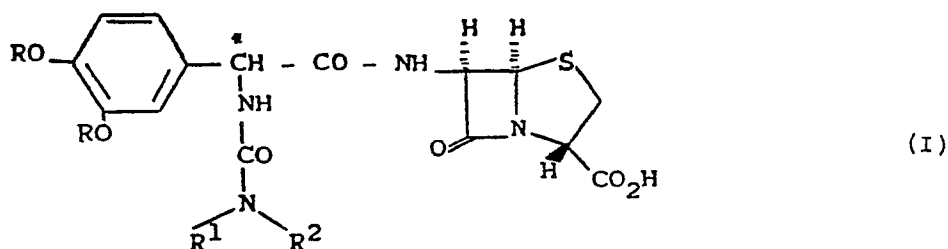
10. Eine Verbindung wie in einem der Ansprüche 1 bis 6 beansprucht, zur Verwendung bei der
65 Behandlung von antibakteriellen Infektionen bei Mensch und Tier.

Revendications

1. Composé de formule (I) ou un sel ou un ester de celui-ci hydrolysable in vivo acceptable du point de vue pharmaceutique:

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15 dans laquelle R est un atome d'hydrogène, un groupe alcoyl(C₁₋₆)carbonyl; R¹ est un atome d'hydrogène ou un groupe alcoyle en C₁₋₆, R² est un atome d'hydrogène ou un groupe alcoyle en C₁₋₆ éventuellement substitué par un groupe hétérocyclyle, un groupe hétérocyclique ou CXR^d où X est O ou S et R^d est un atome d'hydrogène, un groupe alcoyle en C₁₋₆ éventuellement substitué par un groupe hétérocyclyle, ou un groupe hétérocyclyle; ou R¹ et R² forment ensemble avec l'atome d'azote auquel ils sont fixés un groupe hétérocyclyle; les groupes hétérocyclyle mentionnés plus haut comprenant des cycles uniques ou condensés ayant jusqu'à quatre hétéroatomes dans le cycle, choisis parmi des atomes d'hydrogène, d'azote et de soufre et éventuellement substitués avec jusqu'à trois atomes d'halogène, groupes alcoyle en C₁₋₆, alcoxy en C₁₋₆, haloalcoyle en C₁₋₆, hydroxy, amino, carboxy, alcoxy(C₁₋₆)carbonyl, alcoxy-(C₁₋₆)carbonylalcoyle en C₁₋₆, oxo, phényle substitué éventuellement avec jusqu'à trois groupes choisis par des atomes d'halogène, des groupes alcoyle en C₁₋₆, phényle, alcoxy en C₁₋₆, haloalcoyle(C₁₋₆), hydroxy, amino, nitro, carboxy, alcoxy(C₁₋₆)carbonyl, alcoxy(C₁₋₆)carbonylalcoyle en C₁₋₆, alcoxy(C₁₋₆)carbonyloxy, ou alcoyl(C₁₋₆)carbonyl, ou naphthyle, éventuellement substitué de la même façon que le groupe phényle.

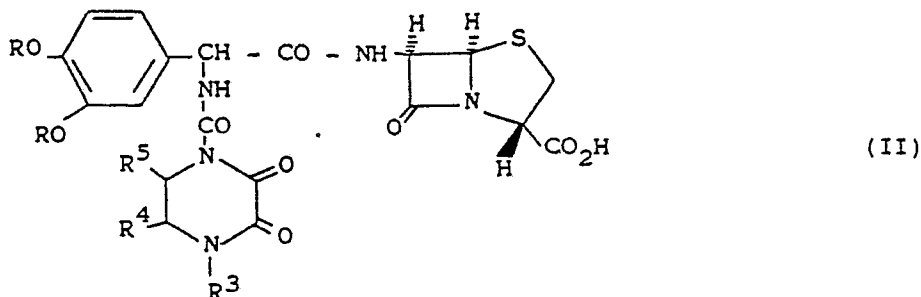
2. Composé suivant la revendication 1, dans lequel R est un atome d'hydrogène ou un groupe acétyl.

30 3. Composé suivant la revendication 1 ou la revendication 2, dans lequel R¹ est un atome d'hydrogène ou un groupe alcoyle en C₁₋₆.

4. Composé suivant la revendication 3, dans lequel R² est un groupe COR^d, où R^d est tel que défini dans la revendication 1.

35 5. Composé de formule (II) ou un sel ou un ester hydrolysable in vivo acceptable du point de vue pharmaceutique de celui-ci:

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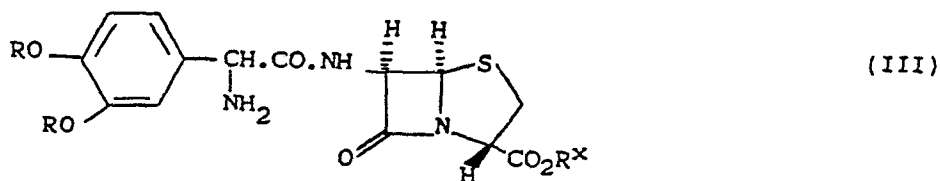
dans laquelle R est tel que défini dans la revendication 1, R³ représente un atome d'hydrogène ou un groupe alcoyle en C₁₋₆; R⁴ et R⁵ sont identiques ou différents et représentent un atome d'hydrogène, un groupe alcoyle en C₁₋₆ ou un atome d'halogène ou un groupe amino, hydroxy ou alcoxy en C₁₋₆.

50 6. Acide 6β-[D-2-(4-éthyl-2,3-dioxopipérazine-1-carbonylamino)-2-(3,4-dihydroxyphényl)]acétamidobisnorpénicillanique;
acide 6β-[D,L-2-(4-éthyl-2,3-dioxopipérazine-1-carbonylamino)-2-(3,4-dihydroxyphényl)]acétamidobisnorpénicillanique;
55 acide 6β-[D,L-2-[3-(3,4-diacétoxyphénylcarbonyl)-3-méthyl-uréido]-2-(3,4-diacétoxyphényl)]acétamidobisnorpénicillanique;
acide 6β-[D,L-2-(3-phénylcarbonyl-3-méthyl-1-uréido)-2-(3,4-dihydroxyphényl)]acétamidobisnorpénicillanique;
acide 6β-[D-2-[3-(4-chlorophénylcarbonyl)-3-méthyl-1-uréido]-2-(3,4-dihydroxyphényl)]-
60 acétamidobisnorpénicillanique ou des sels ou des esters hydrolysables in vivo de ceux-ci acceptables du point de vue pharmaceutique.

7. Procédé de préparation d'un composé suivant la revendication 1, lequel procédé comprend:

A) la réaction d'un composé de formule (III)

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10 dans laquelle R est tel que défini dans la revendication 1, le groupe α-amino est éventuellement substitué avec un groupe qui permet la réalisation de l'acylation et R^x est un atome d'hydrogène ou un groupe bloquant la fonction carboxy, avec un dérivé N-acylant d'un acide de formule (IV)

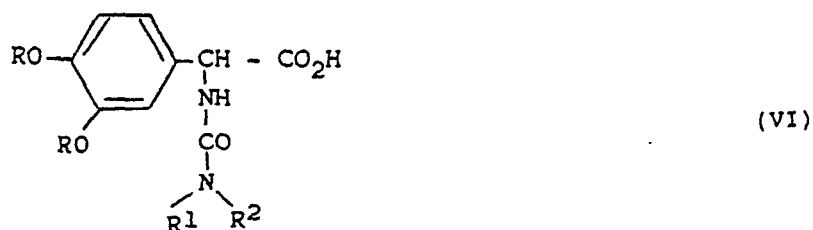


20 dans laquelle R¹ et R² sont tels que définis dans la revendication 1 et de quelconques groupes réactifs pouvant être protégés;

B) la réaction d'un composé de formule (V)



30 dans laquelle le groupe amino est éventuellement substitué avec un groupe qui permet la réalisation de l'acylation et R^x est tel que défini à propos de la formule (III) ci-dessus, avec un dérivé N-acylant d'un acide de formule (VI)



45 dans laquelle R, R¹ et R² sont tels que définis à propos de la formule (I) et de quelconques groupes réactifs peuvent être protégés; et après les étapes A ou B, si cela est nécessaire, la réalisation d'une ou de plusieurs des étapes suivantes:

- i) élimination d'un quelconque groupe R^x qui bloque la fonction carboxy;
- ii) élimination des quelconques groupes protecteurs sur le groupe de la chaîne latérale;
- iii) conversion du produit en un sel ou un ester hydrolysable in vivo de celui-ci.

8. Composition qui comprend un composé suivant l'une quelconque des revendications 1 à 6, avec un support ou un excipient acceptable du point de vue pharmaceutique.

9. Composition suivant la revendication 8, qui comprend aussi un inhibiteur de β-lactamase.

10. Composé suivant l'une quelconque des revendications 1 à 6, utile dans le traitement des infections antibactériennes chez l'homme ou l'animal.